Rapid Drug Desensitization Protocol in Delayed Hypersensitivity Reactions to CFTR Modulator Drugs: When Every Day Counts

Rodríguez-Otero N[1], Fernández-Lozano C[2], Vicente-Santamaría S[3], Díaz-Montalvo L[1], Pérez Menéndez-Conde C[4], Sola-Martínez FJ[1]

[1]*Allergy Department, Ramón y Cajal University Hospital, Ramón y Cajal Health Research Institute (IRYCIS), Madrid, Spain*

[2]*Biochemistry-Research Department, Ramón y Cajal University Hospital, Ramón y Cajal Health Research Institute (IRYCIS), Madrid, Spain*

[3]*Paediatric Gastroenterology, Hepatology and Nutrition and Cystic Fibrosis Section, Ramón y Cajal University Hospital, Ramón y Cajal Health Research Institute (IRYCIS), Madrid, Spain*

[4]*Pharmacy Department, Ramón y Cajal University Hospital, Ramón y Cajal Health Research Institute (IRYCIS), Madrid, Spain*

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Small molecule cystic fibrosis transmembrane regulator (CFTR) modulator drugs have revolutionized the care of cystic fibrosis (CF) patients by targeting the underlying cause, with the aim of slowing disease progression [1]. Currently, there are 2 types of approved CFTR modulators (CFTRm), namely, potentiators (ivacaftor) and correctors (lumacaftor, tezacaftor, elexacaftor). The elexacaftor/tezacaftor/ivacaftor triple combination (ELX/TEZ/IVA), which was approved by the United States Food and Drug Administration in 2019 and European Medicines Agency in 2020, is now available for almost 90% of CF patients (75% in Spain) [1,2]. It has radically changed the course of the disease, with improved lung function and body mass index and reduced pulmonary exacerbations [3]. Safety data have shown good tolerance to the triple combination, although skin rash is frequent in 4%-10% of patients, especially in women in general and in those receiving hormonal contraceptive treatment in particular [3]. Notwithstanding, the risk of allergy to these drugs remains unknown [4].

We report the case of a 9-year-old boy with CF (F508del homozygote), pancreatic insufficiency, and mild lung impairment (baseline FEV_1, 75%). One week after starting therapy with ELX/TEZ/IVA 200/100/150 mg in the morning and IVA 150 mg at night), he presented pruritic, erythematous papules all over his body and face. Within 24 hours, he also developed lip angioedema (Figure). No mucosal involvement or skin blistering was observed, and he had no other symptoms, including fever, respiratory distress, arthralgias, or gastrointestinal complaints. Neither liver involvement nor peripheral blood eosinophilia was recorded. All viral serology results were negative, including parvovirus, measles, cytomegalovirus, and Epstein-Barr virus. Similarly, negative results were recorded in a polymerase chain reaction assay with respiratory samples for coronavirus, influenza virus, and respiratory syncytial virus, as well as *Mycoplasma pneumoniae*. The skin biopsy revealed a spongiotic epidermis without detachment or necrotic keratinocytes. The dermis was slightly edematous, and a mild perivascular lymphohistiocytic inflammatory infiltrate with punctate neutrophils was visible, along with an interstitial component containing abundant neutrophils, occasional eosinophils, and isolated mast cells. There was no leukocytoclasia or fibrinoid necrosis, enabling us to rule out exudative erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Skin lesions improved within 72 hours after high-dose systemic

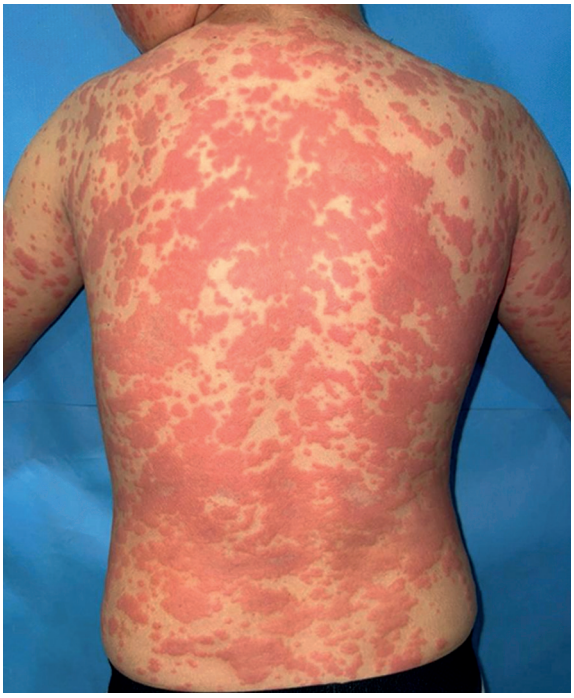

Figure. Erythematous plaques and papules with a tendency to coalesce distributed on the back and blanching under pressure. No epidermal involvement.

corticosteroids and antihistamines and discontinuation of CFTRm. The rash had resolved completely at 3 weeks. An allergy study was performed to determine whether this therapy could be restarted. Since it was not possible to obtain each drug separately, patch tests were performed with IVA, TEZ/IVA, and ELX/TEZ/IVA at 5% and 10% in petrolatum. Patch testing with ELX/TEZ/IVA at 10% was positive (2+) after 48 hours and negative in controls. In order to assess the patient's specific T-cell response to these drugs in vitro, we performed lymphocyte transformation tests (LTTs) with all 3 presentations [4,5]. IVA did not activate the patient's T cells, although an LTT with TEZ/IVA revealed a weakly positive reaction (stimulation index = 2.43 at a concentration of 50 μM) and the LTT with ELX/TEZ/IVA was clearly positive (stimulation index = 4.89 at 50 μM and 5.12 at 20 μM).

An SI between 2 and 3 was considered a weakly positive proliferation response, whereas an SI ≥3 was considered positive [6]. These results suggested that TEZ, ELX, or both activated specific effector T cells. We decided to perform an oral challenge with TEZ/IVA owing to its questionable LTT outcome. After 9 hours, the patient developed a less severe pruritic rash over his thighs and trunk; this subsided with oral corticosteroids and antihistamine. Blood test results were normal. We opted for a slow desensitization protocol with ELX/TEZ/IVA owing to the limited experience with delayed hypersensitivity reactions induced by these therapies [1]. Unfortunately, on the fifth day of desensitization, 4 hours after the intake of 8 mg, a similar rash reappeared on the thighs and spread outwards. Skin lesions improved within 24 hours after an oral corticosteroid and an antihistamine. Finally, following our experience in desensitization to chemotherapy and biological drugs, we designed a rapid drug desensitization (RDD) protocol with ELX/TEZ/IVA and premedication (Supplementary material; table 1), which was successful. CFTRm therapy has been maintained to the present day. Moreover, 1 month after desensitization, the patient had a new best FEV_1 of 94% predicted and reported a clear improvement in his quality of life. Premedication was maintained for the following 2 days at home. Except on 2 occasions, he presented a mild rash that subsided after a few hours with the administration of oral antihistamines. At no time during the introduction of these drugs did we record elevated values for eosinophils or abdominal transaminases, fever, or systemic symptoms. Given the history of severe skin lesions in this case, we performed a half-dose desensitization to ELX/TEZ/IVA (100/50/75 mg) on a single day to assess tolerance, gradually administering the remainder of the dose on another day with the same protocol until doses of 200/100/150 mg were reached. We also proposed to reach therapeutic doses in 1 day for less severe cases. Dilutions were prepared using crushed tablets mixed with ORA-Plus as an aqueous suspension vehicle and ORA-Sweet as a syrup vehicle (1:2 mixture) [7]. One month after desensitization, we obtained a negative LTT result with ELX/TEZ/IVA (Supplementary material; figure 2).

Considering the patient's genetic predisposition, we investigated HLA-A 31:0, a known allele associated with susceptibility to drug reaction with eosinophilia and systemic symptoms syndrome and Stevens-Johnson syndrome in diverse populations. Nevertheless, the findings in this specific case were negative. The patient's HLA typing revealed A:03. Traditionally, the management of delayed drug reactions has involved slow desensitization protocols that extend over several days or even weeks [8]. The underlying mechanism of this process remains unknown [2]. RDD protocols in delayed reactions can efficiently attain the target dose within a brief timeframe, which can prove crucial in many diseases. It has been shown to be a safe procedure when conducted by expert allergists [8]. There is a lack of conclusive evidence regarding the use of premedication either before or after RDD [8,9]. Based on experience with affected patients to date, sensitization to a CFTRm will likely develop if there is a previous history of sensitization to another one [1]. It is imperative to establish adequate personalized multidisciplinary management in these cases.

RDD could be an effective and safe method for patients with delayed hypersensitivity reactions to CFTRm. It enables them to resume therapy swiftly, minimizing periods without treatment, hospital visits, and potential errors at home associated with slower desensitization protocols.

The patient's parents provided their written informed consent for the patient to undergo the desensitization protocol and for the results of the present study to be published.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

ORCID

Natalia Rodríguez-Otero https://orcid.org/0000-0002-2572-7906
Carlos Fernández-Lozano https://orcid.org/0000-0002-4212-4234
Saioa Vicente-Santamaría https://orcid.org/0000-0003-2082-8983
Laura Díaz-Montalvo https://orcid.org/0009-0007-1715-3176
Covadonga Pérez Menéndez-Conde https://orcid.org/0000-0002-7785-0818
Francisco Javier Sola-Martínez https://orcid.org/0009-0004-6207-3843

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Natalia Rodríguez-Otero
Allergy Department, Ramón y Cajal University Hospital,
Ramón y Cajal Health Research Institute (IRYCIS)
M-607, km 9,100
28034 Madrid, Spain
E-mail: nataliarot23@gmail.com

Francisco Javier Sola-Martínez
Allergy Department, Ramón y Cajal University Hospital,
Ramón y Cajal Health Research Institute (IRYCIS)
M-607, km 9,100
28034 Madrid, Spain
E-mail: javier-sola@hotmail.com

